REMARKS

Claims 1-34 were pending in the instant application. Claims 18-34 are withdrawn from consideration as drawn to a non-elected invention. Claims 18-34 (Group II) are related to claims 1-17 (Group I) as product and process of use. It is the Applicant's understanding that, once the pending product claims are found allowable, any non-elected process claims (Group II, claims 18-34) will be rejoined and examined if such process claims include all of the limitations of the elected product claims (MPEP §821.04).

Claims 1-2 have been amended. Accordingly, claims 1-34 will be pending after entry of the instant amendment. Applicants reserve the right to prosecute the claims as originally filed in this or a continuing application. Support for the claim amendments can be found throughout the claims and specification as originally filed. No new matter has been added.

Priority Claim

The Examiner states that claims 3-9 are only entitled to a priority date of November 26, 2003, the filing date of the instant application. The Examiner states that the claims do not receive the benefit of the prior applications 60/426,982 (hereafter the '982 application), 60/458,051 (hereafter the '051 application) and 60/430,517 (hereafter the '517 application) because they do not provide adequate support for the claims. In particular, the Examiner states that the '517 application "does not contemplate siRNA targeted to a mutant allele wherein the antisense strand comprises a sequence comprising one or more modified bases positioned opposite the point mutations." Applicants respectfully disagree. Applicants submit that the '517 application provides ample support for claims 3-9 as presently recited, and that claims 3-9 are thus fully entitled to a priority date of the '517 application, March 26, 2003.

The '517 application teaches that siRNAs "can be used to selectively down-regulate the expression of an allele (e.g., a mutant), even when the allelic mRNA differs from a second allele (e.g., wild-type) by only a ***single nucleotide***, as is the case with certain ***mutations***," such as "***dominant, gain-of-function type of gene mutations***, including, but not limited to, ALS" (pages 3-4, bridging paragraph). The '517 application explicitly teaches that the siRNAs of the invention "are ***capable of single nucleotide discrimination*** and selectively down-regulating expression of their target alleles" (pages 3-4, bridging paragraph).

The '517 application further describes characteristics of siRNAs useful for single nucleotide discrimination. For example, the '517 application teaches that "one strand of the siRNA is an ***antisense strand that is complementary, e.g., fully complementary***, to a section of about 16 to 30 or more nucleotides of the ***mRNA of the target gene*** or target allele" (see page 2, lines 15-17). The '517 application further teaches that "within the scope of the present method is the use of ***modified siRNAs to selectively target one allele***" (page 5, lines 16-17). In particular, the '517 application teaches specific base modifications in the antisense strand which are used when exemplary point mutations, *e.g.*, an adenine or uracil/thymine, are present in the target mRNA:

> Where the mutation results in the ***replacement of a base in the target mRNA with an adenine***, siRNAs modified with ***U(5Br) or U(5I) in the antisense strand are generally used***. Where the mutation results in ***the replacement of a base target RNA with a uracil*** (***thymine*** in the DNA), siRNAs modified with ***DAP in the antisense strand are generally used***. (page 5, lines 17-20)

The position of a modified base in an siRNA relative to a particular nucleotide in the target mRNA is further described in Figure 4. Figure 4 describes sequences of the sense and antisense strands of an siRNA directed against Green Fluorescent Protein mRNA, as well as the sequence of the GFP target mRNA. The positions of base modifications in the siRNA are indicated, where lines below the antisense strand indicate adenine bases modified with DAP, and triangles indicate uracils modified to U(5I) or U(5Br). In particular, Figure 4 shows adenine bases modified with DAP in the antisense strand of the siRNA ***positioned opposite each uracil*** in the target mRNA (thymine in DNA) and further shows U(5Br) or U(5I) in the antisense strand of the siRNA ***positioned opposite each adenine*** in the target mRNA.

The '517 application further teaches the principle underlying the instant invention, *e.g.*, the biochemical principle governing why a modified base in the siRNA antisense strand placed opposite a point mutation in the mRNA target of the mutant allele would allow selective suppression of the mutant allele as compared to the wild type allele by the modified siRNA:

> Without wishing to be bound by theory, it is believed that the ***favorable binding interactions between the mutant/target mRNA and the modified siRNA*** and the ***less favorable binding interactions between the wild-type mRNA and the***

> ***modified siRNA*** cause the modified siRNAs to bind preferentially to the mutant target mRNA, leaving the wild-type mRNA untouched. (page 5, first paragraph)

Based on the teachings in the specification, one of skill in the art would recognize that a preferential binding between a ***modified siRNA*** and mutant mRNA as compared to that between the ***modified siRNA*** and wild type mRNA, where the mutant and wild type mRNA differ by as little as one nucleotide, would involve base pairing between the modified base and the point mutation in the target mutant mRNA.

In view of the foregoing, Applicants submit that, contrary to the Examiner's assertion, the '517 application clearly contemplates an siRNA targeted to a mutant allele wherein the antisense strand comprises ***a sequence comprising one or more modified bases positioned opposite the point mutations***. Accordingly, claims 3-9 are fully entitled to a priority date of the '517 application, March 26, 2003.

Claim Rejections Under 35 USC § 112

Claims 3-17

Claims 3-17 are rejected as failing to comply with the written description requirement. In particular, the Examiner contends that "the specification does not provide adequate written description of a siRNA targeted to a sequence comprising point mutations and that directs allele-specific cleavage of an mRNA encoded by a mutant allele. Therefore, in only disclosing siRNA compounds that are targeted to a gene encoding GFP and RFP and disclosing siRNA compounds that inhibit expression of GFP and RFP, the specification does not provide information on what siRNA compound directs allele-specific cleavage of a mRNA encoded by the mutant allele." The Examiner continues, "for example, what siRNA structure or sequence would one skilled in the art know or expect would direct allele-specific cleavage of an mRNA encoded by a mutant allele wherein the point mutation is an adenine or a thymine."

Applicants respectfully traverse this rejection. Applicants submit that the specification provides sufficient description so as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention as presently recited.

The fundamental factual inquiry in a written description rejection is whether the claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed. The subject matter of the claim ***need not be described literally*** (i.e. using the same terms or in haec verba) in order for the disclosure to satisfy the written description requirement. MPEP 2163.02. Rather, the inquiry into whether the written description requirement is met must be determined on a case-by-case basis and is a question of fact. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976).

Claim 3, and claims 4-17 which depend therefrom, are drawn to a small interfering RNA (siRNA) comprising a sense strand and an antisense strand, wherein the ***sense strand comprises a sequence homologous to a region of a mutant allele encoding a gain-of-function mutant protein***, said ***region comprising one or more point mutations***, and wherein the ***antisense strand comprises a sequence comprising one or more modified bases positioned opposite the point mutations***, such that the siRNA directs allele-specific cleavage of a mRNA encoded by the mutant allele.

The critical structural feature of the presently claimed siRNAs is the presence in the antisense strand of a ***modified base positioned opposite a point mutation in a target mRNA*** encoded by a mutant allele. Given this feature, one of ordinary skill in the art is put in possession of a broad variety of siRNA compounds that direct allele-specific cleavage of a mRNA encoded by a mutant allele. Indeed, the specification provides ample teaching as to the sequence and structure of siRNAs which can be used for allele-specific cleavage of an mRNA encoded by a mutant allele.

For example, Applicants teach numerous examples of diseases caused by dominant, gain-of-function gene mutations, including Alzheimer's disease, Huntington's disease, Parkinson's disease and ALS (see, *e.g.*, pages 18-19). One of skill in the art would recognize that the sequences of the mutant alleles responsible for these diseases were known and easily obtainable at the time of filing the instant application. Further, the specification provides at pages 8-16 and, in particular, at pages 10-11, detailed guidance for selecting the sequences of siRNA molecules to target a particular mutant allele:

> 1. Beginning with an AUG start codon, search for AA dinucleotide sequences; each AA and the 3' adjacent 16 or more nucleotides are potential siRNA targets. ***The siRNA should be specific for a target region that differs by at least one base pair between the wild type and mutant allele, e.g., a target region comprising***

> ***the gain-of-function mutation. In cases where the gain-of-function mutation is associated with one or more other mutations in the same gene, the siRNA can be targeted to any of the mutations.*** In some cases, the siRNA is targeted to an allelic region that does not comprise a known mutation but does comprise an allelic variation of the wild-type (reference) sequence. The first strand should be complementary to this sequence, and the other strand is identical or substantially identical to the first strand. ***In one embodiment, the nucleic acid molecules are selected from a region of the target allele sequence beginning at least 50 to 100 nt downstream of the start codon, e.g., of the sequence of SOD1***. Further, siRNAs with lower G/C content (35-55%) may be more active than those with G/C content higher than 55%. Thus in one embodiment, the invention includes nucleic acid molecules having 35-55% G/C content. In addition, the strands of the siRNA can be paired in such a way as to have a 3' overhang of 1 to 4, *e.g.*, 2, nucleotides. Thus in another embodiment, the nucleic acid molecules can have a 3' overhang of 2 nucleotides, such as TT. The overhanging nucleotides can be either RNA or DNA.
>
> 2. Using any method known in the art, compare the potential targets to the appropriate genome database (human, mouse, rat, etc.) and eliminate from consideration any target sequences with significant homology to other coding sequences. One such method for such sequence homology searches is known as Basic Local Alignment Search Tool (BLAST), which is available at the National Institutes of Health (NIH)/National Library of Medicine's (NLM's) National Center for Biotechnology Information (NCBI) website.
>
> 3. Select one or more sequences that meet your criteria for evaluation. Further general information about the design and use of siRNA may be found in "The siRNA User Guide," available at the Max Planck Institute for Biophysical Chemistry website.

The specification further provides detailed guidance for choosing modified bases and the positions at which modified bases are placed in the siRNAs of the invention:

> Where the mutation results in the ***replacement of a base in the target mRNA with an adenine***, siRNAs modified with ***U(5Br) or U(5I) in the antisense strand are generally used***. Where the mutation results in ***the replacement of a base target RNA with a uracil*** (***thymine*** in the DNA), siRNAs modified with ***DAP in the antisense strand are generally used***. (pages 7-8, bridging paragraph)

Thus, based on the present specification, one of ordinary skill in the art would have recognized that Applicants had possession of the claimed invention at the time of filing.

Indeed, it is firmly established that the descriptive text needed to meet the Written Description requirement varies with the nature and scope of the invention at issue, and with the

scientific and technologic knowledge already in existence. *Capon v. Eshhar*, 418 F.3d 1349, 1357 (Fed. Cir. 2005). In *Capon*, the Federal Circuit explained that "since the law is applied to each invention in view of the state of the relevant knowledge, its application will vary with differences in the state of knowledge in the field and differences in the predictability of the science." *Id.* Specifically, the Court stated that:

> Precedent illustrates that the determination of what is needed to support generic claims to biological subject matter ***depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter***. *Id.* at 1359 (emphasis added).

The Court further explained that "the written description may be satisfied 'if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure.'" *Id.* (citing *Amgen Inc. v. Hoechst Marion Roussel*, Inc., 314 F.3d 1313, 1332 (Fed. Cir. 2003) (emphasis added)). Accordingly, "[a]s each field evolves, the balance also evolves between what is known and what is added by each inventive contribution." *Id.* at 1358.

Based on the foregoing considerations and framework for written description articulated by the Federal Circuit, the subject matter of the pending claims drawn to an siRNA that directs allele-specific cleavage of a mRNA encoded by a mutant allele, wherein the sense strand comprises a sequence homologous to a region of the mutant allele encoding a gain-of-function mutant protein, said region comprising one or more point mutations, and wherein the antisense strand comprises one or more modified bases positioned opposite a point mutation, are fully described in accordance with 35 U.S.C. §112, first paragraph, by the present specification. For example, with respect to the existing knowledge in the field at the time the present application was filed, it was well-known how to select siRNA molecules targeting a particular gene sequence. Further, the level of skill in the art and the maturity of the technology of generating siRNA molecules, including siRNAs containing base modifications, were high at the filing date of the present application.

Accordingly, for at least the foregoing reasons, it would have been clear to one of ordinary skill in the art based on the present specification that Applicants' had full possession of

the claimed invention at the time of filing. Applicants therefore respectfully request the Examiner to reconsider and withdraw this rejection under 35 U.S.C. §112, first paragraph.

Claims 6-7

Claims 6-7 are rejected as being indefinite in the recitation of "wherein the point mutation." The Examiner states that there is insufficient antecedent basis for this limitation in the claims because claims 6-7 are dependent on claim 4, which depends from any one of claims 1-3, and claims 1-2 do not recite point mutations." Claims 1-2 have been amended to recite "point mutations," thereby obviating the rejection.

Claim Rejections Under 35 USC § 102(e)

Claims 1-2, 4-5 and 10-17

Claims 1-2, 4-5 and 10-17 are rejected as lacking novelty in view of Tuschl *et al.* (WO 02/44321). The Examiner relies on Tuschl *et al.* for teaching "a siRNA 19-25 nucleotides in length (see page 4, lines 1-5)" and "a composition comprising a siRNA and a pharmaceutically acceptable carrier (see page 9, lines 11-16)." The Examiner relies on Tuschl *et al.* for further teaching an "siRNA comprising at least one modified base wherein the modified base comprises 5-bromouracil or 5-iodouracil (page 5, lines 23-31)." Applicants respectfully traverse this rejection. The cited reference fails to teach each and every element of the present invention as recited in the claims.

The instant claims are drawn to siRNAs having specified structural and functional limitations. In particular, claim 1 is drawn to an siRNA comprising at least one ***modified base***, wherein the modified base is ***capable of enhancing single nucleotide discrimination*** between a first target having 1, 2, 3 or more point mutations relative to a second target. Claim 2 is drawn to a small interfering RNA (siRNA) ***capable of single nucleotide discrimination between a first and second allele***, the first allele having 1, 2, 3 or more point mutations relative to the second allele, wherein the siRNA comprises at least ***one modified base*** capable of ***enhancing binding interactions between the siRNA and mRNA encoded by the first allele when compared with binding interactions between the siRNA and mRNA encoded by the second allele***. Claims 4-5 and 10-17 depend from claims 1 or 2. In addition to the recited structural limitations in these

claims, the recited functional limitations of ***enhancing nucleotide discrimination*** (*e.g.*, selective suppression of the mutant allele as compared to the wild type allele by the modified siRNA) or ***enhancing binding interactions between the siRNA and mRNA encoded by the mutant allele,*** connote further structure to the claimed siRNAs. Indeed, as discussed above, the instant specification teaches that siRNAs useful for single nucleotide discrimination between a mutant and wild type allele comprise an antisense strand that comprises ***a sequence comprising one or more modified bases positioned opposite the point mutations.*** Moreover, the specification teaches the biochemical principle underlying why such a structure mediates single nucleotide discrimination.

Tuschl *et al.* is generally directed to siRNA molecules useful for mediating RNA interference. Tuschl *et al.* report that "in order to further ***enhance the stability*** [of an siRNA], the 3' overhangs may be ***stabilized against degradation***" and continue that "[a]lternatively, substitution of pyrimidine nucleotides by modified analogues... is tolerated and does not affect the efficiency of RNA interference" (page 5, first paragraph). Tuschl *et al.* report that "[p]referred nucleotide analogues are selected from sugar- or backbone-modified ribonucleotides" and continue that "[i]t should be noted, however, that also nucleobase-modified ribonucleotides... *e.g.*... uridines or cytidines modified at the 5-position, *e.g.*, 5-(2-amino)propyl uridine, 5-bromo uridine; adenosines and guanosines modified at the 8-position, *e.g.*, 8-bromo guanosine; deaza nucleotides, *e.g.*, 7-deaza-adenosine; O- and N-alkylated nucleotides, *e.g.* N6-methyl adenosine are suitable" (page 5, third paragraph). Applicants respectfully note that Tuschl *et al.* fail to teach 5-iodouracil, as state by the Examiner.

For a prior art reference to anticipate a claimed invention in terms of 35 U.S.C. § 102, the prior art must teach **each and every element** of the claimed invention. Lewmar Marine v. Barient, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987).

Tuschl *et al.* fail to teach or suggest an siRNA comprising a modified base for any purpose other than to increase stability. Indeed, Tuschl *et al.* fail to teach or suggest an siRNA comprising a modified base useful for ***enhancing single nucleotide discrimination*** or for ***enhancing binding interactions*** between the siRNA and mRNA encoded by a mutant allele. In particular, Tuschl *et al.* fail to teach or suggest the ***positioning*** of a modified base in the ***antisense strand*** of an siRNA ***opposite a point mutation in the target mRNA*** of a mutant allele. Thus the teachings of Tuschl *et al.* fail to anticipate the instant claims.

In view of the foregoing, Applicants respectfully request that the rejection of claims 1-2, 4-5 and 10-17 under 35 § 102(e) be reconsidered and withdrawn.

Claims 3-5 and 9

Claims 3-5 and 9 are rejected as lacking novelty in view of Xu *et al.* (US 2004/0192629). The Examiner relies on Xu *et al.* for teaching "a siRNA comprising a sequence homologous to a region of a mutant allele encoding SOD1, a mutant protein involved in ALS disease, wherein the antisense strand comprises a sequence positioned opposite a point mutation (see Figure 1)" and for further teaching that "the siRNA can comprise a modified base at any position (see paragraph 0039)."

Applicants submit that Xu *et al.* is not available as a 102(e) reference against the instant invention with regard to the disclosure of an siRNA comprising a modified base. As discussed above, claims 3-5 and 9 are entitled to a priority date of March 26, 2003. The Xu *et al.* application claims priority to two U.S. patent applications, one of which has a filing date preceding the priority date of the instant claims (US Application No. 60/423,507, filed November 4, 2002) and a second having a filing date following the priority date of the instant claims (U.S. Application No. 60/488,283, filed July 18, 2003). Applicants note that the teaching that an siRNA can comprise a modified base as disclosed in US 2004/0192629 is not disclosed in the earliest priority document. Accordingly, the Xu *et al.* disclosure of an siRNA containing a modified base can only be entitled to a filing date of the second priority application, *i.e.*, July 18, 2003, which is well after the priority date of the instant claims. Applicants therefore respectfully request that the rejection of claims 3-5 and 9 under 35 U.S.C. § 102(e) as anticipated by Xu *et al.* be reconsidered and withdrawn.

Claim Rejections Under 35 USC § 103(a)

Claims 3-5, 7 and 9 are rejected under 35 U.S.C. §103(a) as being obvious over Xu *et al.* (US 2004/0192629) in view of Buhr *et al.* (US 6,476,205). The Examiner relies on Xu *et al.* for the reasons set forth above. The Examiner acknowledges that Xu *et al.* fail to teach "a siRNA comprising a modified base [that] is 2,6-diaminopurine."

The Examiner further relies on Buhr *et al.* for teaching "an oligonucleotide with a 2,6-diaminopurine modified base" and "to modify nucleobases in antisense oligonucleotides" where such modifications "increase an antisense compound's resistance to degradation." The Examiner concludes that "it would have been obvious to one of ordinary skill in the art to incorporate modifications as taught by Buhr *et al.* into said siRNA compounds," that "one would have been motivated to modify said siRNA compounds as taught by Buhr *et al.* because Buhr *et al.* teach that such modifications increase an antisense compound's resistance to degradation" and that "one would have a reasonable expectation of success given that Buhr *et al.* teach the stability of the modified oligonucleotide compounds."

Applicants submit that Xu *et al.* is not available as a 103 reference against claims 3-5, 7 and 9 with regard to the disclosure of an siRNA comprising a modified base for the same reasons discussed above regarding the novelty rejection in view of Xu *et al.* As discussed above, claims 3-5, 7 and 9 are entitled to a priority date of March 26, 2003. Also as set forth above, the Xu *et al.* disclosure of an siRNA containing a modified base can only be entitled to a filing date of the second priority application, *i.e.*, July 18, 2003, which is well after the priority date of the instant claims. Applicants therefore respectfully request that the rejection of claims 3-5, 7 and 9 under § 103(a) be reconsidered and withdrawn.

In view of the above amendments and remarks, it is believed that this application is in condition for allowance. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

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Respectfully submitted,

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